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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/719,493	11/21/2003	Arthur M. Krieg	C1039.70021US01	3218

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EXAMINER	
TUNGATURTHI, PARITHOSH K	

ART UNIT	PAPER NUMBER
1643	

MAIL DATE	DELIVERY MODE
08/31/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/719,493	KRIEG ET AL.	
	Examiner	Art Unit	
	Parithosh K. Tungaturthi	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 June 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *42-53 and 56-78* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *42-53 and 56-78* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The applicant has timely traversed the non-final rejection in the reply filed on 06/11/2007, and a response to the arguments is set forth.

2. Claims 1-41 have been cancelled.

3. Claim 60 has been amended.

4. Claims 42-53 and 56-78 are under examination.

Objections Withdrawn

5. The objection of claim 60 is withdrawn in view of amendments to the claim.

Rejections Maintained

6. Claims 42-53 and 56-78 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The applicants argue that the cited references in the previous office action are not predictable of CpG oligonucleotides which are already demonstrating promise in clinical trials. For example, Agarwal does not suggest that CpG DNA is not useful therapeutically ... "it is evident that CpG DNA is a powerful tool to modulate the immun system and can be exploited to treat a wide variety of diseases..." (page 7 of the

response filed on 06/11/2007, in particular). The applicants argue that the fact that only limited data is available in human clinical trials does not suggest that the invention would not work. The applicants further argue that it is not proper for the examiner to require clinical data to support the enablement of the invention ... applicants generated pre-clinical data on CpG oligonucleotides that demonstrated activity consistent with the treatment of cancer (page 8 of the response filed on 06/11/2007, in particular). Significant amounts of data demonstrating the specific effects of CpG oligonucleotides are provided in the specification ... the description and the data found in the specification establish a pattern to establish a pattern of immune stimulation which is consistent with the treatment of cancer (pages 9-10 of the response filed on 06/11/2007). One skill in the art would simply need to follow the guidance provided in the specificaiotn using a class of molecules which is comeercially available or easily synthesized (page 11 of response filed on 06/11/2007).

The above arguments are carefully considered, but are not found persuasive.

Agarwal (Cited in PTO-892 mailed on 09/01/2005) clearly teaches that although the presence of unmethylated CpG dinucleotide is essential for the induction of immunostimulatory activity (page 114, 2nd column in particular) and that the induction of cytokines in vivo depends on the sequences flanking the CpG dinucleotide, as well as the dose, the route of administration and the host animal species (page 116 1st column, in particular). The applicants point to page 116 of Agarwal, specifically 2nd column last sentence, wherein it is taught that CpG DNA elicit effects at $\mu g\ kg^{-1}$ doses; such

statement does enable a skilled in artisan to design the dose of administration of CpG molecules in the treatment of cancer. Further, Agarwal concluded the unpredictability in treatment of cancer comprising administering CpG dinucleotide only after a series of experimental studies as discussed in the publication. Further, the specification neither provides guidance required to enable one skilled in the art to treat cancer comprising administering CpG dinucleotide nor provides significant data testing many CpG containing dinucleotide for the treatment of cancer. Although, the specification established a pattern of immune stimulation by this class of oligonucleotides and such induction of cytokines may be involved in the cancer regression; the correlation between the induction of the three disclosed cytokines and treatment of cancer has not been clearly established. Agarwal, (published in 2002) well after the filing date of the instant application, teach that that the medicinal chemistry of CpG DNA have just begun and needs further fine-tuning, which clearly indicates that at the time of filing of the instant application the applicants were not enabled for the claimed invention, which is a method of treating various cancers comprising administering CpG immunostimulatory oligonucleotides. Further, the unpredictability of the treatment of cancer is supported by Peterson et al, Schuh et al, Bibby et al and Siajo et al (Cited in PTO-892 mailed on 07/19/2006). The references cited above, individually, teach that the numerous agents that show exciting activity in preclinical models have had minimal activity clinically.

MPEP 2164.03:

> The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches

> exactly how to make or use the invention ... if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling.
>
> In particular, the court in In re Marzocchi, 439 F.2d 220, 223-24, 169 USPQ 367, 369-70 (CCPA 1971), stated: [I]n the field of chemistry generally, there may be times when the well-known unpredictability of chemical reactions will alone be enough to create a reasonable doubt as to the accuracy of a particular broad statement put forward as enabling support for a claim. This will especially be the case where the statement is, on its face, contrary to generally accepted scientific principles. Most often, additional factors, such as the teachings in pertinent references, will be available to substantiate any doubts that the asserted scope of objective enablement is in fact commensurate with the scope of protection sought and to support any demands based thereon for proof ... in applications directed to inventions in arts where the results are unpredictable, the disclosure of a single species usually does not provide an adequate basis to support generic claims. In re Soll, 97 F.2d 623, 624, 38 USPQ 189, 191 (CCPA 1938). In cases involving unpredictable factors, such as most chemical reactions and physiological activity, more may be required.

Thus, since the prior art cited clearly communicates the unpredictability in the treatment of cancers and since the specification does not provide a skilled artisan the guidance to practice such; the claimed invention requires an undue experimentation. In response to the applicants arguments that "applicants generated pre-clinical data on CpG oligonucleotides that demonstrated activity consistent with the treatment of cancer", the specification is viewed merely as an invitation to one skilled in the art to develop the claimed invention because the specification fails to disclose any guidance, direction, or working examples for the treatment of cancer comprising CpG oligonucleotides.

> MPEP 2164.05(a):
>
> Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. In deciding *In re Fisher*, 166 USPQ

> 18, 24 (CCPA 1970), the Court indicated the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. "Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention." *Genentech Inc. v. Novo Nordisk A/S*, 42 USPQ2d 1001, 1005 (CA FC 1997).

Therefore, it is the examiners position that the specification fails to teach how to make and use the claimed invention without undue experimentation and that the scope of any enablement provided to one skilled in the art is not commensurate with the scope of protection sought by the claims.

The applicants submit Krieg et al (Exhibit 1) and Krieg et al (Exhibit 2) in support of enablement of CpG molecules for treatment of cancer.

Both Krieg et al references cited by the applicant teach the mechanisms and therapeutic application of activating TLR9 with synthetic CpG oligodeoxynucleotide (ODN) agonists. The applicants are pointed to 2nd column, page 1192 of Krieg et al (Exhibit 1) wherein it is taught that tumor have multiple means of suppressing or evading antitumor immunity, and it remains unclear to what extent TLR9 activation will be able to overcome these defenses and improve survival ... it will be necessary to use combinations of synergistic therapies to achieve the full clinical potential of this approach; and that further studies into the effects of various chemotherapy regimes on immune function might make it possible to design combination therapies that will predictably provide greater clinical benefit to patients.

Hence, there exists a high unpredictability in the extrapolation of promising preclinical data to predict clinical efficacy in the field of treatment of cancers, in addition to the undue experimentation required to conclude the application of the claimed CpG molecules in the treatment of cancer. As such, a showing that the CpG molecule that acts as a TLR9 agonist results in promising preclinical results is not sufficient to enable a skilled artisan to practice the claimed invention. The applicant did not demonstrate by argument and/or evidence that the disclosure, as filed, would have enabled the claimed invention for one skilled in the art at the time of filing.

The description and the data found in the specification is not sufficient, because the specification does not teach those skilled in the art how to make and use the full scope of the claimed invention, which is the treatment of cancer comprising administering CpG immunostimulatory oligonucleotides comprising 8 to 100 nucleotides in length, without undue experimentation. The examples in the specification show that unmethylated CpG are effective at stimulating B-cell proliferation, cytokine secretion for example; however, based on the undue experimentation necessary in understanding the treatment of cancer comprising CpG molecules as taught by Agarwal and because Zips et al teach that the prediction of drug effects in cancer patients based solely on *in vitro* data is not reliable and further evaluation in animal tumor systems is essential. The amount of additional experimentation is deemed to be undue because in order to practice the claimed invention with a reasonable expectation of success, one of skill in the art would have to show evidence overcoming art recognized problems that the

broadly claimed CpG-containing oligonulceotides would not work for treating or preventing any cancer.

Thus, in conclusion, the applicant is reminded that the high degree of unpredictability recognized in the art, particularly the required characteristics of the immunostimulatory oligonucleotide in order to be an effective in vivo immunostimulatory oligonucleotide; the breadth of the claims as mentioned above; the limited number of working examples and guidance in the specification; and the high degree of skill required, it is concluded that the amount of experimentation required to perform the broadly claimed vaccine composition is undue. The references clearly point towards the undue experimentation needed in practicing the treatment of cancers comprising CpG molecules.

Thus, The instant application gives no data relevant to the use of the nucleic acids mentioned in the claims in any in vivo method to control or affect any of the conditions mentioned in the claims. One skill in the art would be compelled to perform undue experimentation in order to practice the claimed invention because of the large number of variables connected with the use of such nucleic acids. For example, the instant application does not give guidance as to the type of administration, the times or frequencies of administration, or the dosages required to obtain desired effects.

Conclusion

7. No claims are allowed.

8. **THIS ACTION IS MADE FINAL**. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Parithosh K. Tungaturthi whose telephone number is 571-272-8789. The examiner can normally be reached on Monday through Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry R. Helms, Ph.D. can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,
Parithosh K. Tungaturthi
(571) 272-8789

DAVID J. BLANCHARD
~~PATENT~~ EXAMINER
PRIMARY